Insulin Levels and the Natural History of Glucose Intolerance in Nauruans

Gary K. Dowse, Paul Z. Zimmet, and Veronica R. Collins

Longitudinal changes in serum insulin concentrations in relation to the natural history of glucose intolerance and factors associated with the incidence of NIDDM were studied in 838 nondiabetic Micronesian Nauruans over the 5.1-year period from 1982 to 1987. In 13 individuals who had data at three time-points and who developed NIDDM only at the final test, 2-h insulin levels followed an inverted V-shaped pattern as glucose tolerance declined to NIDDM. Subjects who were normal (n = 651) or had impaired glucose tolerance (IGT) (n = 187) at the 1982 baseline survey were divided into six natural history categories depending on glucose tolerance in 1987. Changes in glucose tolerance were accompanied by changes in mean 2-h insulin concentration that paralleled the inverted V pattern seen in the 13 individuals. Longitudinal changes in fasting insulin were less consistent, but mean levels increased as subjects developed NIDDM. The 5.1-year incidence of NIDDM was strongly related to baseline fasting and 2-h glucose concentrations, but associations with insulin levels were weak and inconsistent. Neither fasting nor 2-h insulin concentrations contributed to logistic regression models predicting deterioration in glucose tolerance, whereas fasting and 2-h glucose levels were included in all models and BMI also predicted deterioration from normal. These data showing sequential changes in insulin concentrations support the β-cell exhaustion theory of NIDDM pathogenesis. However, in contrast to glucose concentrations and obesity, insulin levels are poor predictors of NIDDM risk in Nauruans. This reflects the complexity of interactions with other metabolic markers and the inability of a single examination to characterize the point along the inverted V curve of insulin secretion that an individual has reached. *Diabetes* 45:1367–1372, 1996

Cross-sectional data from several populations have demonstrated an inverted U- or V-shaped relationship between plasma glucose concentrations and measures of insulin secretion (1–5). This relationship has been interpreted as a representation of the pathogenetic sequence leading to the development of NIDDM. Thus, the apex of the curve corresponds with the point at which the over-worked pancreatic β-cell decompensates, resulting in a further rise in plasma glucose levels and overt NIDDM (4–6).

From the International Diabetes Institute, Melbourne, Australia.

Address correspondence and reprint requests to Dr. Gary Dowse, Midwest Public Health Unit, P.O. Box 68, Geraldton WA 6531, Australia.

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IGT, impaired glucose tolerance.

This interpretation has been supported by incidence data in which the risk of NIDDM has been studied in relation to insulin response within the broad categories of normal and impaired glucose tolerance (IGT) in a range of populations (7–10). Furthermore, longitudinal data for 7 rhesus monkeys (11) and 11 Pima Indians (12) have confirmed that sequential changes in insulin secretion and glucose tolerance in individuals follow a course whereby insulin secretion initially increases and then decreases as glucose tolerance deteriorates.

Nauruans have a particularly high risk of NIDDM (13), and data from this population have provided some of the earliest epidemiological support for the pancreatic decompensation theory (8). We have examined incidence data for a much larger group of Nauruans that extend the earlier findings from this and other populations. We demonstrate changes in insulin and glucose concentrations according to natural history categories for all study subjects and for a subgroup of subjects developing NIDDM for whom we have data at several time-points. Finally, we have investigated optimal predictors of NIDDM in Nauruans.

RESEARCH DESIGN AND METHODS

Study population. Nauru is a small isolated island in the central Pacific Ocean. The indigenous Micronesian population of approximately 5,500 persons (1987) are highly susceptible to obesity and NIDDM. A series of health surveys have been performed in 1975–1976, 1982, and 1987, as described previously (13). The entire adult Nauruan population was eligible for the 1982 survey, with 1,561 respondents giving a response rate of 83% (14). All subjects who had attended either or both of the 1975–1976 and 1982 surveys were eligible to attend the 1987 follow-up. The overall response rate was 86%, and of these glucose tolerance was classifiable in 93% (n = 1,201) (13). The current study of longitudinal changes in serum insulin concentrations and glucose tolerance is limited to the 838 subjects who had normal or impaired glucose tolerance at the 1982 baseline. Of these, 13 individuals who had developed NIDDM by 1987 also had 2-h insulin data in both 1975–1976 and 1982.

Survey procedure. The classification of NIDDM and IGT was based on World Health Organization criteria utilizing a fasting 75-g oral glucose tolerance test, with venous plasma collected fasting and at 2 h (15). Glucose was measured in Nauru from fresh plasma with a YSI analyzer (YSI, Yellow Springs, OH) in both 1982 and 1987, while in 1975–1976 frozen samples were transported to Melbourne for later analysis (13,14,16,17). NIDDM was defined by a self-reported history that was confirmed by *a*) diagnostic fasting (≥7.8 mmol/l) or 2-h postload (≥11.1 mmol/l) glucose concentrations and/or *b*) treatment with hypoglycemic medication. In the absence of a history, a 2-h glucose level ≥11.1 mmol/l was required. IGT was defined by a 2-h glucose level 7.8–11.0 mmol/l, plus a fasting glucose level <7.8 mmol/l.

Weight and height were measured by standard methods, and BMI was calculated as weight (in kilograms) divided by the height (in meters) squared. Insulin concentrations were measured in duplicate by radioimmunoassay on samples that had been stored at -20°C in Melbourne. For the 1975–1976 study, insulin was assayed in plasma by the method of Herbert et al. (4,18). The 1982 and 1987 stored sera were assayed together using commercial kits (Amersham, UK). It was not possible to compare directly the 1975–1976 insulin assay with that used in 1982 and 1987. However, comparing overall population levels of the two assays in normal subjects suggested that the

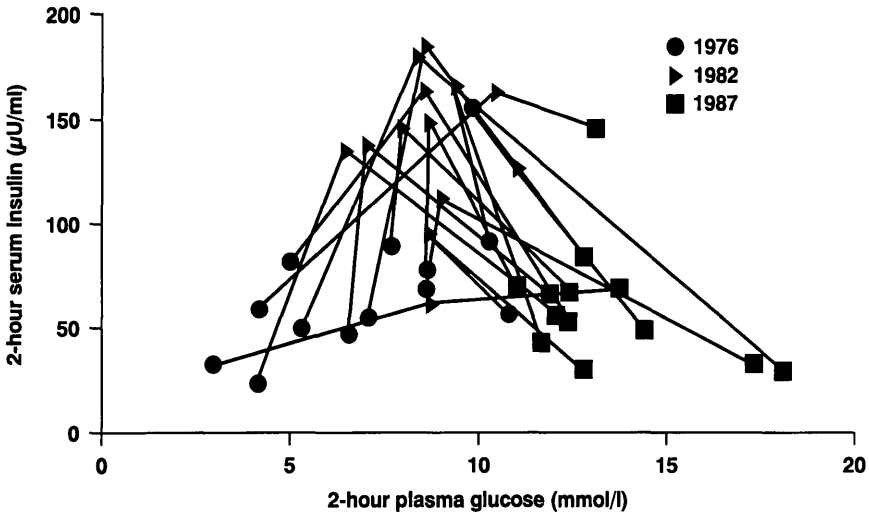

FIG. 1. Longitudinal changes in 2-h serum insulin and plasma glucose concentrations in 13 Nauruans who were diagnosed with NIDDM in 1987 and who also had data for 1975–1976 and 1982.

1975–1976 method underestimated 2-h insulin levels, as measured using the Amersham kits, by around 22%. This difference was insufficient to explain the observed changes in insulin concentration between 1975–1976 and 1982.

Statistical analysis. Analyses were performed using SPSS PC+ software (19). To study longitudinal changes in insulin and glucose concentrations, individual or mean values were examined in relation to particular natural history categories and time-points. Insulin and glucose values were $\log_{10}$-transformed and geometric mean values are shown. Differences in values at each time-point were assessed by analysis of variance. Cumulative incidence of NIDDM between 1982 and 1987 (5.1 years) was examined across the range of glucose values and by quintiles of insulin and BMI levels that were determined separately for the normal and IGT groups in 1982.

Logistic regression (backwards stepwise) (19) was used to investigate the relative importance of insulin and glucose concentrations and other risk factors for changes in glucose tolerance between 1982 and 1987. Separate models were computed for *1*) normal subjects progressing to NIDDM, *2*) IGT to NIDDM, *3*) all nondiabetic subjects to NIDDM, and *4*) IGT to normal. Independent variables were age, BMI, and fasting and 2-h plasma glucose and serum insulin concentrations (continuous) and sex and self-reported family history in a first-degree relative (categorical). Insulin × glucose interaction terms were tested in all models.

RESULTS

Longitudinal changes in insulin. Two-hour insulin concentrations were available at three time-points (1975–1976, 1982, and 1987) for 13 Nauruans who developed NIDDM at the final examination. In 9 of 13 cases, there was an inverted V-shaped relationship between insulin and glucose (Fig. 1). In one individual who had a 2-h glucose concentration of 9.9 mmol/l at the first examination, insulin declined in both subsequent tests. In an additional two cases, the rise in 2-h insulin between 1975–1976 and 1982 was associated with a modest improvement in glucose tolerance (within the IGT range), but in both there was a typical descending limb between 1982 and 1987. In the 13th case, 2-h insulin levels did not decline in absolute terms as glucose tolerance deteriorated to NIDDM.

Subjects who were normal (n = 651) or IGT (n = 187) at the 1982 baseline were divided into six natural history groups depending on glucose tolerance in 1987. Mean insulin and glucose concentrations for each of these groups are plotted in Fig. 2. Changes in glucose tolerance were accompanied by changes in 2-h insulin levels that conformed to an inverted V pattern, and the vectors tended to parallel the V formed by the mean values of the individuals with data at three time-points. On the normal to IGT axis, changes in insulin secretion and glucose tolerance occurred in both directions. Among subjects with IGT at baseline, those who returned to normal had the highest mean 2-h insulin levels (NS), the lowest 2-h glucose ($P < 0.0001$), and the largest fall in mean 2-h insulin levels. The smallest change in glucose and insulin

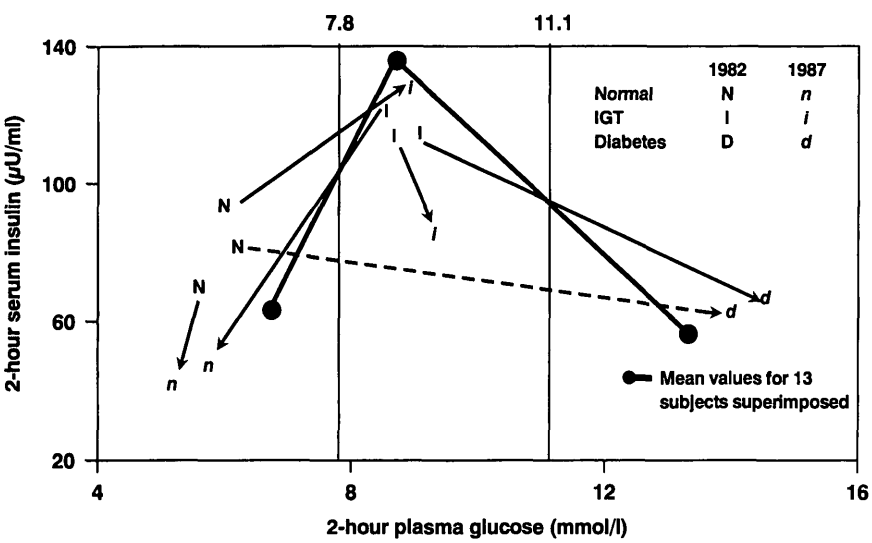

FIG. 2. Longitudinal changes in geometric mean 2-h serum insulin and plasma glucose concentrations between 1982 and 1987 for 838 nondiabetic Nauruans according to six natural history categories: normal-normal (n = 559); normal-IGT (n = 65); normal-NIDDM (n = 27); IGT-normal (n = 77); IGT-IGT (n = 52); and IGT-NIDDM (n = 58). Geometric mean values for individuals with data for all three surveys (see Fig. 1) are superimposed.

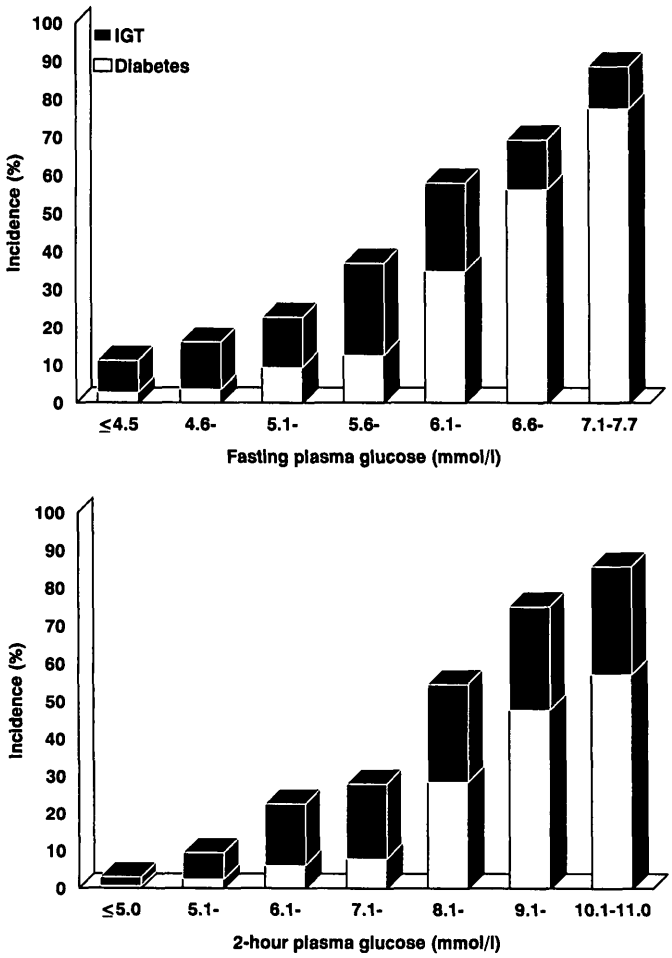

FIG. 3. Five-year cumulative incidence (1982–1987) of NIDDM and IGT in nondiabetic Nauruans according to baseline plasma glucose concentrations. Top: fasting values. Bottom: 2-h values.

concentrations was observed in the group who remained IGT. Movement from normal to NIDDM directly was associated with a small decline in absolute mean 2-h insulin levels.

The relationship between fasting glucose and insulin levels in the six new NIDDM subjects for whom data were available from the three surveys was inconsistent. The development of NIDDM in 1987 was associated with both increasing and decreasing basal insulin, although mean levels increased. The vectors traced by the normal to IGT and the IGT to NIDDM natural history categories were also associated with increasing mean fasting insulin levels (data not shown).

Predictors of NIDDM. There was a clear relationship of the 5.1-year cumulative incidence of NIDDM with increasing fasting (χ^2_1 [trend] = 108.2, $P < 0.001$) and 2-h (χ^2_1 = 140.7, $P < 0.001$) glucose concentrations (Fig. 3). Associations were of similar strength for the incidence of all glucose intolerance (NIDDM or IGT). The risk of NIDDM increased substantially at 2-h levels >8 mmol/l, and fasting levels >5.6 mmol/l.

Cumulative incidence was also examined across normal- and IGT-specific quintiles of fasting and 2-h insulin, and BMI (Fig. 4). Among subjects with normal glucose tolerance, risk of NIDDM was positively associated with BMI (χ^2_1 = 16.7, $P < 0.001$) and fasting (χ^2_1 = 14.7, $P = 0.001$) but not with 2-h ($P = 0.09$) insulin, while there was a significant trend for deterioration to "NIDDM or IGT" associated with each of these variables ($P < 0.001$). By contrast, for the subgroup with IGT at baseline, there was little or no relationship of NIDDM incidence with 2-h insulin ($P = 0.8$), fasting insulin ($P = 0.06$), or BMI ($P = 0.3$).

The simultaneous effect of insulin and glucose concentrations on the 5.1-year incidence of NIDDM for all subjects who where nondiabetic in 1982 was also examined (data not shown). Within any quintile of either fasting or 2-h insulin, increasing glucose levels were clearly associated with increased risk of NIDDM. The converse was not true: for subjects with normal glucose tolerance or low levels of fasting glucose, insulin levels did not appear to influence risk. However, there was a U-shaped pattern of risk associated with insulin levels for subjects within the upper quantile of 2-h (8.8–11.0 mmol/l) or fasting (5.6–7.7 mmol/l) glucose concentrations.

Baseline fasting and 2-h glucose concentrations were retained in all logistic models predicting NIDDM (Table 1). For subjects with IGT, only glucose levels were selected, but BMI also contributed to models predicting deterioration from normal. Age (younger) was an independent predictor only for the model predicting deterioration from normal directly to NIDDM. When all subjects who were nondiabetic at baseline were considered, the only significant independent predictors of NIDDM were BMI and fasting and 2-h glucose levels, although sex and family history were of marginal importance. Younger age, lower BMI, and lower glucose values predicted reversion from IGT to normal.

Neither fasting nor 2-h insulin concentrations contributed to the models, except for a negative relationship of 2-h insulin in the normal-to-NIDDM model. However, when repeated with 2-h insulin modeled as a categorical variable, the relationship was sinusoidal, not linear. Insulin-glucose interaction terms did not improve any of the models.

DISCUSSION

The prevalence of NIDDM appears to be increasing worldwide, particularly in developing populations (20–22). Hence, there is great interest in clarifying the pathogenesis of the disease and in defining predictive markers. This study shows that longitudinal changes in 2-h insulin levels in Nauruans are in accord with the hypothesis of β-cell decompensation in NIDDM pathogenesis (6,23). However, insulin was clearly inferior to glucose levels and BMI in predicting NIDDM.

Natural history. In individuals and in grouped data, declining glucose tolerance in Nauruans was associated first with increasing and then decreasing 2-h insulin levels in an inverted U- or V-shaped pattern. Within the normal and IGT range, improving glucose tolerance was associated with a decrease in 2-h insulin, suggesting that factors responsible for the initially higher insulin response and glucose intolerance had improved. The subgroup of IGT subjects who returned to normal were less obese and had lower 2-h glucose levels than those who progressed to NIDDM. Unfortunately, there is no infor-

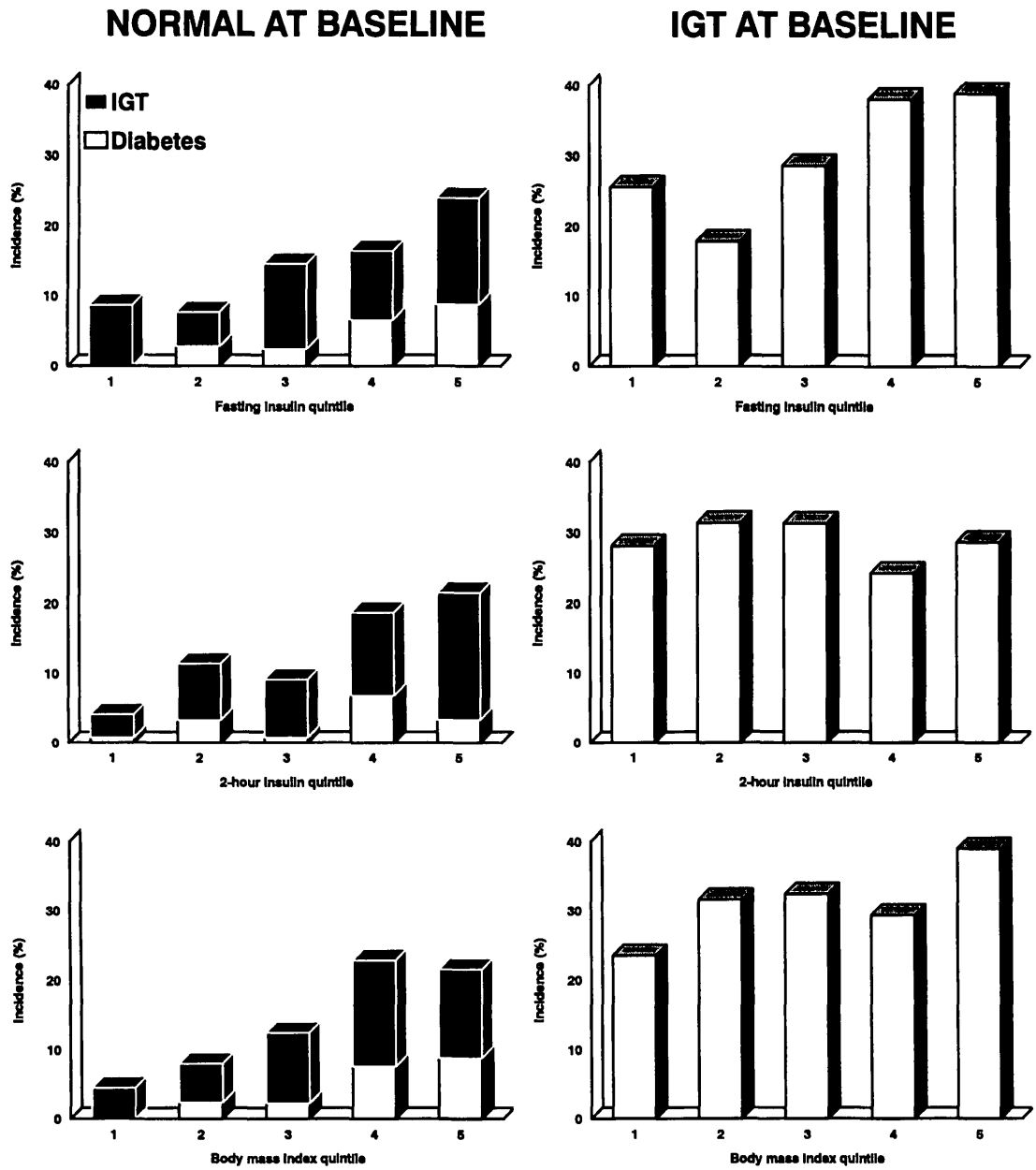

FIG. 4. Five-year cumulative incidence (1982–1987) of NIDDM in Nauruans with normal (left) or impaired (right) glucose tolerance at baseline, in relation to quintiles of fasting serum insulin (top), 2-h serum insulin (middle), and BMI (bottom).

mation about whether these subjects changed their diet or exercise habits between surveys.

The inverted V-shaped relationship between insulin response and glucose tolerance demonstrated in the 13 Nauruans who developed NIDDM is consistent with cross-sectional data from this (4) and other populations (1–3,5) and with similar longitudinal observations in 11 Pima Indians (12). Hansen and Bodkin's data for fasting insulin levels in seven monkeys (11) and acute and late insulin responses in five monkeys (24) also support an inverted U-pattern. For fasting insulin, sequential changes varied between Nauruans (not shown), as they did in Pima Indians (12), but in both populations the mean or median levels increased as subjects moved from normal to newly diagnosed NIDDM. With a longer duration of diabetes, basal insulin eventually fell in monkeys (11,24) and Pima Indians (12) but later than the fall that was observed in insulin response.

Predictors of NIDDM. In Nauruans, obesity was an independent predictor of the deterioration in glucose tolerance in all but the IGT-to-NIDDM model, and even when insulin was forced into models, its importance was undiminished. Obesity also predicted the deterioration from normal, but not from IGT, in Pima Indians. It was suggested that this was so because its effect in IGT subjects was mediated through insulin resistance (23). The lack of importance of obesity in the progression from IGT in Nauruans and Pima Indians is not consistent with data from leaner populations (7,10) and may reflect the ubiquity of obesity in IGT subjects in these populations.

An earlier and smaller study in Nauruans found that higher 2-h insulin levels predicted the deterioration from normal independently of glucose concentrations and

TABLE 1
Optimal multiple logistic regression models predicting 5.1-year incidence of NIDDM in Nauruans

Model or variable	Odds ratio	95% CI	*P* value
Normal to NIDDM*			<0.0001
Age	0.91	0.83–0.99	0.033
Sex (female)	0.28	0.08–0.98	0.046
BMI	1.18	1.09–1.28	<0.001
Fasting glucose	2.73	1.02–7.34	0.047
2-h glucose	4.40	1.97–9.84	<0.001
2-h insulin	0.98	0.97–1.00	0.037
IGT to NIDDM†			<0.0001
Fasting glucose	2.42	1.37–4.27	0.002
2-h glucose	1.78	1.14–2.77	0.012
Normal or IGT to NIDDM‡			<0.0001
Sex (female)	0.54	0.28–1.03	0.062
BMI	1.07	1.02–1.12	0.003
Positive family history	1.77	0.95–3.31	0.072
Fasting glucose	2.31	1.43–3.72	<0.001
2-h glucose	2.16	1.72–2.71	<0.001
IGT to normal§			<0.0001
Age	0.97	0.95–1.00	0.047
BMI	0.94	0.89–1.00	0.038
Fasting glucose	0.57	0.34–0.97	0.040
2-h glucose	0.48	0.30–0.77	0.002

Odds ratios were calculated for increments of 1 year in age, 1 mmol/l in glucose, 1 μU/ml in insulin, and 1 kg/m^2 in BMI. Variables included in models are described in METHODS. *Dependent variable for model 1 was NIDDM vs. normal; for normal to NIDDM, n = 521, cases = 17, and model χ^2 = 53.8 (6 df). †For IGT to NIDDM, n =162, cases = 46, and model χ^2 = 26.2 (2 df). ‡For normal or IGT to NIDDM, n =741, cases = 63, and model χ^2 = 145.2 (5 df). §For IGT to normal, n =162, cases = 68, and model χ^2 =33.5 (4 df).

BMI, whereas among subjects with IGT the risk of NIDDM was highest in those with relatively lower 2-h insulin levels (8). Similar results have been demonstrated for normal subjects in Pima Indians (23) and for IGT subjects, independent of glucose concentrations, in Japanese (7) and Pima Indians (9,23). Ironically, it appears that while the interpretations regarding insulin secretion in the pathogenesis of NIDDM that were based on the results of the earlier Nauru study (8) were correct, the particular findings of the predictive potential of insulin were serendipitous. In this larger study, 2-h insulin was a poor predictor of the deterioration from normal and IGT.

Fasting insulin was a similarly poor predictor of NIDDM in Nauruans and in Japanese IGT subjects (7), but in Pima Indians it predicted the deterioration from normal and IGT independent of 2-h glucose levels. A small study in Mexican-Americans found that fasting insulin levels predicted NIDDM in nondiabetic subjects independent of fasting glucose levels, but it was not clear whether the relationship held if 2-h glucose levels were controlled (25). These authors suggested that insulin and glucose concentrations might be used as screening tests to identify subjects at risk of NIDDM in whom preventive measures could be targeted. The data for Nauruans indicate that glucose values and BMI are much clearer indicators, and the added expense of measuring insulin concentrations is unlikely to improve prediction.

There may be several reasons for the lack of importance of insulin as a predictor in this study of Nauruans, compared with the earlier report (8) and the studies in Pima Indians (9,23), which are most comparable methodologically. Inconsistencies within and between studies of NIDDM incidence may follow from the complex associations between risk factors and metabolic markers, variable speeds at which individuals develop the disease, and differences in progress along the pathogenetic pathway at the time of examination (24). In obese Japanese, for example, lower insulin response did not predict the deterioration from IGT, in contrast to results for leaner subjects (7). The Nauruan IGT group were almost uniformly obese, and were more obese than in the earlier (8) or Pima Indian (9,23) studies. As obese subjects presumably follow a relatively rapid course to NIDDM, it may be that insulin responses had not yet fallen at the time of the baseline examination in the subgroup who proceeded to NIDDM.

Two-hour insulin is an imperfect indicator of insulin response, and more direct measures of early and late insulin secretion might have greater predictive potential. However, published data are inconsistent, reflecting the difficulties of using cross-sectional snap-shots as predictors in a longitudinal process. Kadowaki et al. (7) found that the mean 30- and 60-min increments in insulin secretion were lower in IGT subjects who progressed to NIDDM. Similarly, a low acute insulin response predicted NIDDM in Pima Indians (26), and in cross-sectional studies, first-degree relatives of NIDDM subjects had diminished first-phase insulin secretion (27). By contrast, first- and second-phase insulin secretion were positively associated with NIDDM incidence in the offspring of two diabetic parents (28). As shown in monkeys, these results are not incompatible, since acute and late insulin responses in that species also followed an inverted-U course in the evolution of NIDDM. Hence, the result of a particular study probably depends on the sum effect of where individuals lie along the curve at the time of the baseline investigation, irrespective of the measure of insulin secretion (24).

There is general consensus that defects in both insulin sensitivity and secretion are involved in the pathogenesis of NIDDM, but there is debate as to which of these defects may be primary or at least of greatest importance (6,23–28). The most widely supported hypothesis is that insulin resistance (a product of genetic and environmental factors including obesity, exercise, and diet) leads to glucose intolerance and compensatory insulin hypersecretion. Ultimately, in some individuals, insulin secretion fails, again dependent on an interaction of heredity and other factors, including glucose toxicity and age (6,23,26). However, there is evidence that dysfunctional (not necessarily deficient) β-cell response may precede changes in insulin sensitivity in rodents (29), monkeys (11,24), and humans (30,31).

Irrespective of the nature of the initiating lesion, the evidence from diverse ethnic groups and study designs indicates that, in individuals destined to develop NIDDM,

insulin secretion initially rises and then falls as glucose tolerance declines. This inverted U- or V-shaped curve is seen clearly in Nauruans. However, because of this complex relationship and interactions with other factors determining susceptibility to NIDDM, insulin levels themselves are poor predictors of individual susceptibility. Glucose concentrations and obesity are much stronger predictors of the deterioration in glucose tolerance in this population.

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